New 2H-Azirin-3-amines as Synthons for Sulfur-Heterocyclic -Amino Acids

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New 2*H*-Azirin-3-amines as Synthons for Sulfur-Heterocyclic α-Amino Acids

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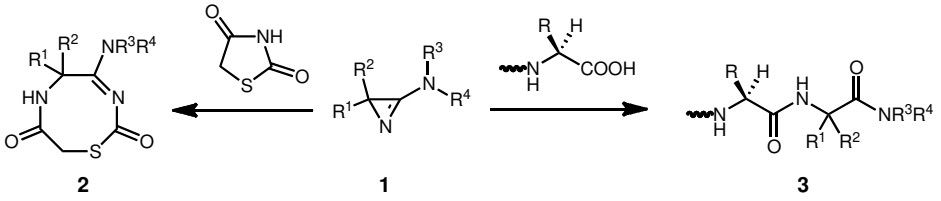
Abstract

Three new spiroheterocyclic 2*H*-azirin-3-amines, which contain a sulfur atom, were prepared and successfully used for the synthesis of oligopeptides containing sulfur-heterocyclic α-amino acids via the 'azirine/oxazolone method'.

Introduction

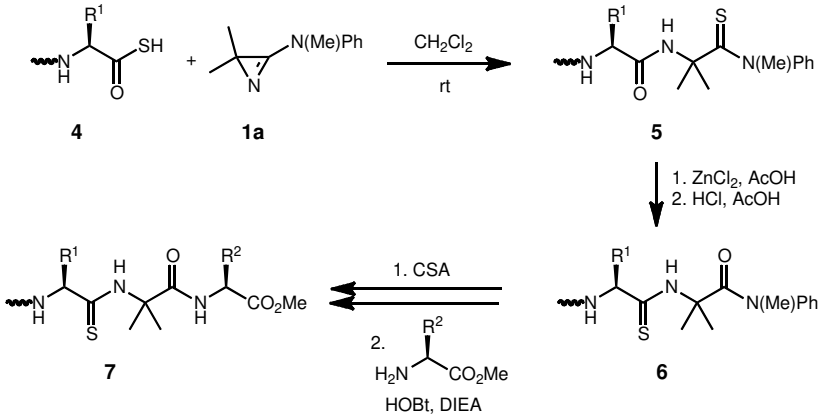
Since the first report on the preparation of 2,2-disubstituted 2*H*-azirin-3-amines **1** by *Rens* and *Ghosez*,[1] these cyclic amidines have been shown to be useful synthons for α,α-disubstituted α-amino acids in syntheses of heterocycles and peptides.[2] For example, the reaction with thiazolidine-2,4-dione leads to the thiadiazocine derivatives **2** via a ring enlargement reaction,[3] whereas the reaction with a peptide acid yields the chain-extended peptide amide **3** with a terminal 2,2-disubstituted glycine residue[4] (*Scheme 1*). The latter reaction was used extensively for the synthesis of conformationally restricted natural and artificial oligopeptides.[5]

Scheme 1



The so-called 'azirine/oxazolone method' has also been modified successfully for the synthesis of endothiopeptides of type **7** containing α,α-disubstituted α-amino acids[6] (*Scheme 2*). Thus, thiocarboxylic acids or peptides with a terminal –COSH group react with, *e.g.*, **1a** to give thioamides **5** with an extended peptide chain. Subsequent acid-catalyzed isomerization via a 1,3-thiazole intermediate yields **6**, which can be further coupled with amino acid esters.

Scheme 2



With the aim of preparing synthons for sulfur-containing heterocyclic α-amino carboxylic acids, new spiroheterocyclic 2*H*-azirin-3-amines were synthesized and used in model reactions.

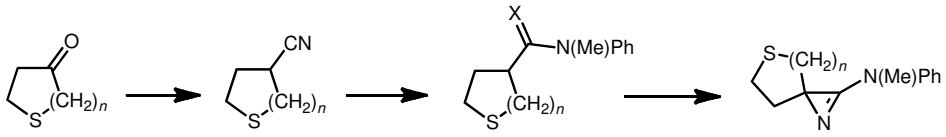
Results

The original synthesis of 2*H*-azirin-3-amines **1** starts from *N*,*N*-disubstituted 2,2-dialkyl-acetamides. The reaction with phosgene in toluene followed by addition of a base like Et_3N leads to α-chloroenamines, which on treatment with NaN_3 in ether yield **1**.[1] As in some cases the reaction of amides with phosgene was sluggish, a modified protocol via the corresponding

thioamides was developed.[7] Furthermore, it was shown that the selective hydrolysis of products **3** of the azirine coupling with a –N(Me)Ph group occurred already at room temperature.[8] Finally, a phosgene-free one-pot synthesis of **1a** was elaborated via formation of the Li-enolate of the *N*-methyl-*N*-phenyl 2,2-dialkylacetamide and subsequent treatment with diphenyl phosphorochloridate (DPPCl) and NaN_3 in THF.[9]

With these methods we synthesized sulfur-containing spiroheterocyclic 2*H*-azirin-3-amines **1b** and **1c**, starting with tetrahydrothiophene-3-one (**8a**) and tetrahydrothiopyran-4-one (**8b**), respectively (*Scheme 3*). Transformation to the nitriles **9** by treatment with Tosmic[10] or in a three-step process via $NaBH_4$ reduction, tosylation, and substitution with NaCN,[11] followed by saponification and amide formation via the acid chloride[10] or DCC coupling,[11] yielded the amides **10**. The latter were used for the azirine synthesis via the Li-enolates[10] or, after formation of the thioamide by treatment with Lawesson reagent, via the phosgene method.[11]

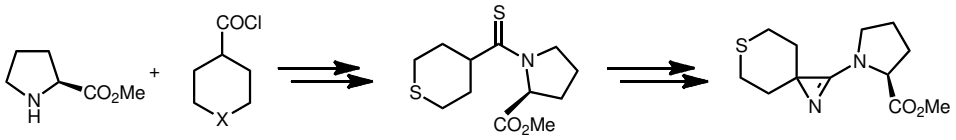
Scheme 3



8a *n* = 1 **8b** *n* = 2 **9** **10** **1b** *n* = 1 **1c** *n* = 2

In an analogous manner, the sulfur-heterocyclic dipeptide synthon **1d** was prepared via the thioamide **11**[12] (*Scheme 4*).

Scheme 4

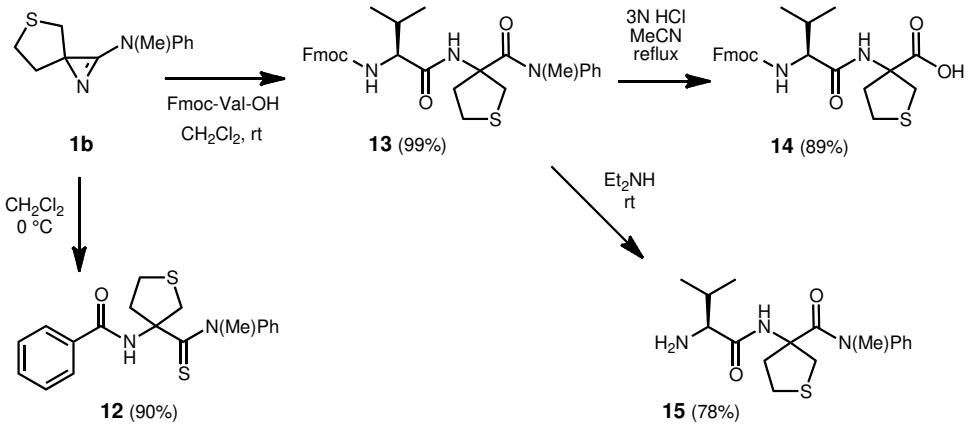


11 **1d**

The reactivity of the new 2*H*-azirin-3-amines **1b**–**1d** is similar to that of earlier prepared analogues. For example, the reaction of **1b** with thiobenzoic acid in CH_2Cl_2 at 0 °C led to the

corresponding S-heterocyclic *N*-benzoyl α-aminothiocarboxamide **12** in high yield[11] (*Scheme 5*).

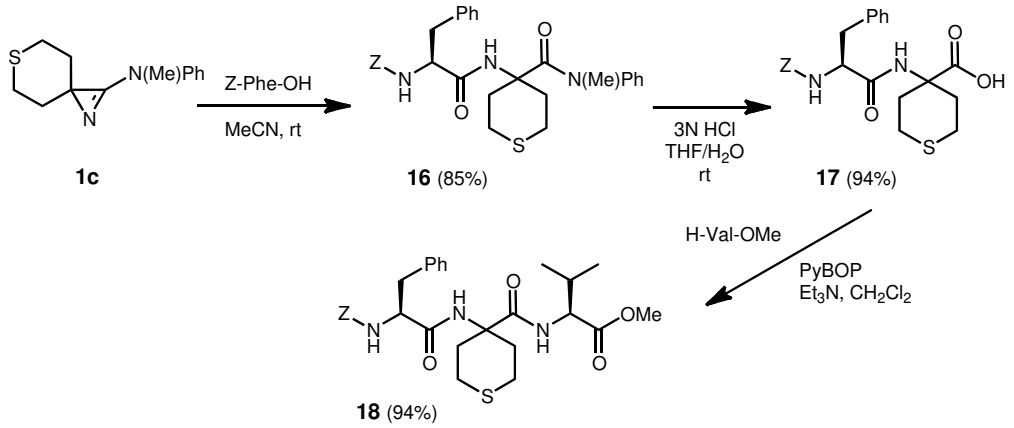
Scheme 5



With the aim of demonstrating the usefulness of **1b**–**1d** as synthons for sulfur-heterocyclic α-amino acids in the preparation of sterically congested peptides, reactions with various N-protected α-amino acids or peptide fragments were performed. Thus, reaction of **1b** (Tht-synthon) with Fmoc-Val-OH in CH_2Cl_2 at rt gave the protected dipeptide amide **13** as a 1:1 mixture of two diastereoisomers, which could be separated by column chromatography. Then, **13** was deprotected selectively at the C- and N-terminus by treatment with 3N HCl in MeCN/H_2O and Et_2NH, respectively, leading to **14** or **15**[11] (*Scheme 5*). These dipeptides are suitable building blocks in the synthesis of oligopeptides.

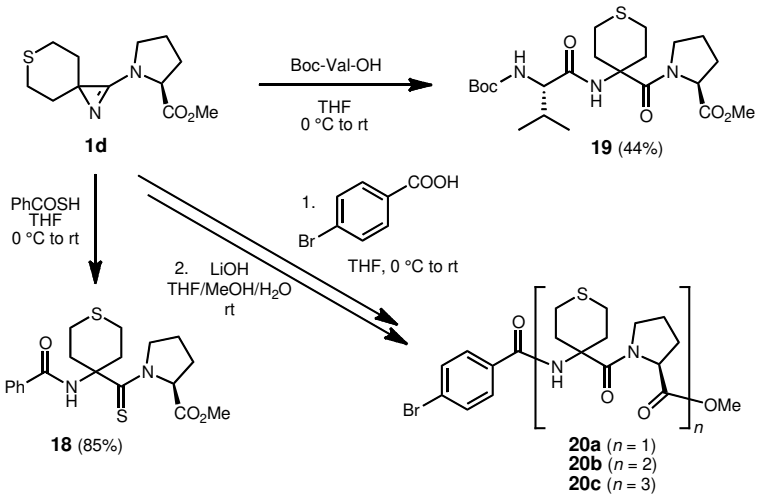
Similarly, **1c** (Thp-synthon) was reacted with various N-protected α-amino acids.[10,13] For example, coupling with Z-protected Phe-OH gave **16**, followed by selective hydrolysis of the terminal amide group (3N HCl, THF/H_2O, rt) to yield **17**. The latter was coupled with H-Val-OMe by standard methods to give **18** (*Scheme 6*). It was shown by X-ray crystallography and by ^{1}H-NMR studies that these tripeptides form a β-turn in the crystalline state as well as in solution, stabilized by an intramolecular hydrogen bond between NH of valine and C=O of the protecting group.

Scheme 6



Finally, the reaction of **1d** (Thp-Pro-synthon) with thiobenzoic acid occurred smoothly in THF at room temperature to give the endothiodipeptide **18**, whereas the reaction with protected α-amino acids such as Boc-Val-OH led to tripeptides, *e.g.* **19**[12] (*Scheme 7*). It is important to note that **19** in the crystal adopts a conformation, which is almost identical with a β-turn in spite of the fact that no stabilization by an intramolecular hydrogen bond is possible. This may be explained by the presence of the α,α-disubstituted α-amino acid in analogy to the effect of aminoisobutyric acid (Aib; see ref.[14]).

Scheme 7



The coupling reaction of **1d** with 4-bromobenzoic acid gave **20a**, and subsequent saponification of the ester group led to the corresponding dipeptide acid, which was again reacted with **1d**, yielding tetrapeptide ester **20b**. Repetition of these two steps led to the hexapeptide **20c** in good yield (*Scheme 7*). It was shown by X-ray crystallography and ^{1}H-NMR studies that these highly congested oligopeptides also exist in a helical conformation in the crystalline state as well as in solution.

Conclusions

The new sulfur-containing 2*H*-azirin-3-amines can be prepared conveniently and have been shown to be useful building blocks for novel heterocyclic α,α-disubstituted α-amino acids in the synthesis of conformationally restricted oligopeptides. On the basis of the general reactivity of 2*H*-azirin-3-amines, they may also be used for the synthesis of novel sulfur containing heterocycles.

Acknowledgement

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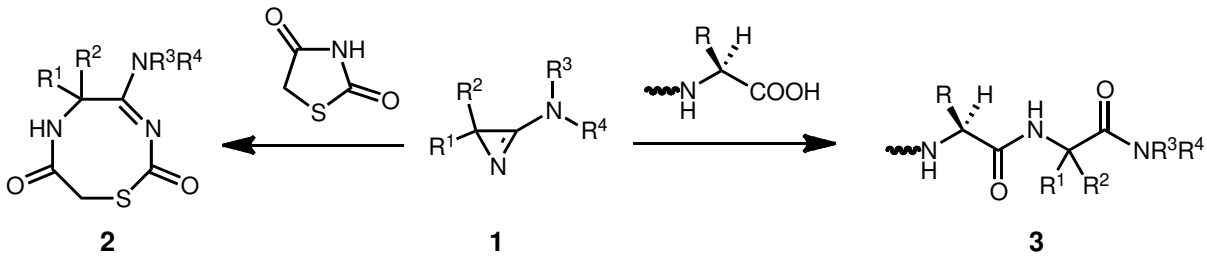
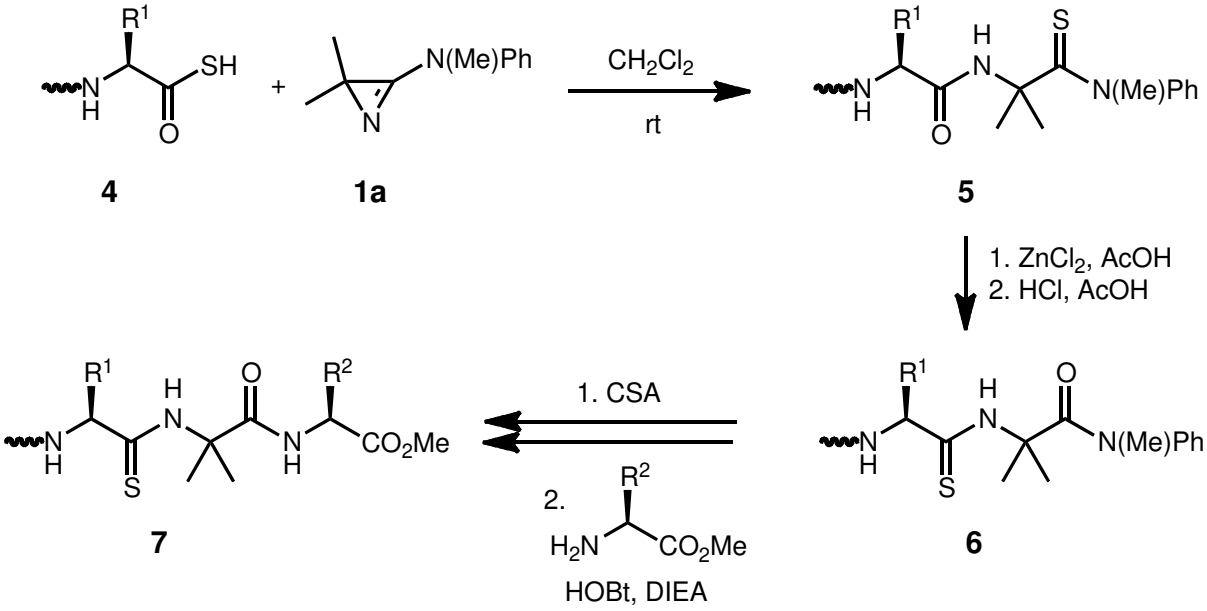


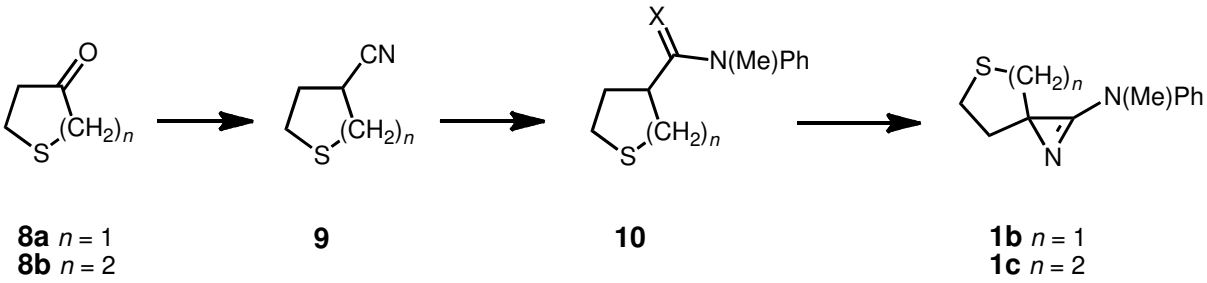
2 **1** **3**

Scheme 1



4 **1a** **5** **7** **6**

Scheme 2

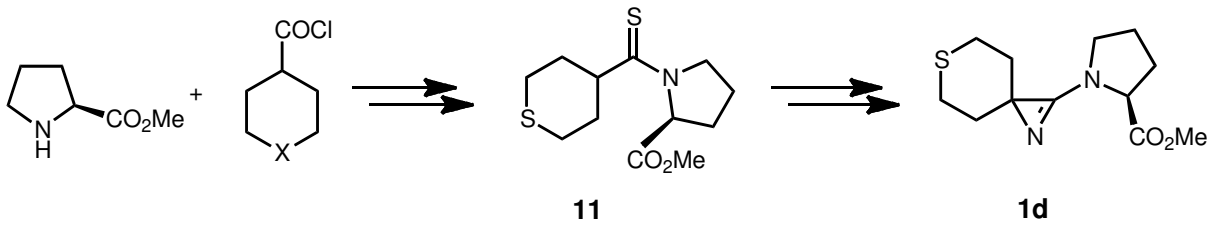


8a *n* = 1
8b *n* = 2

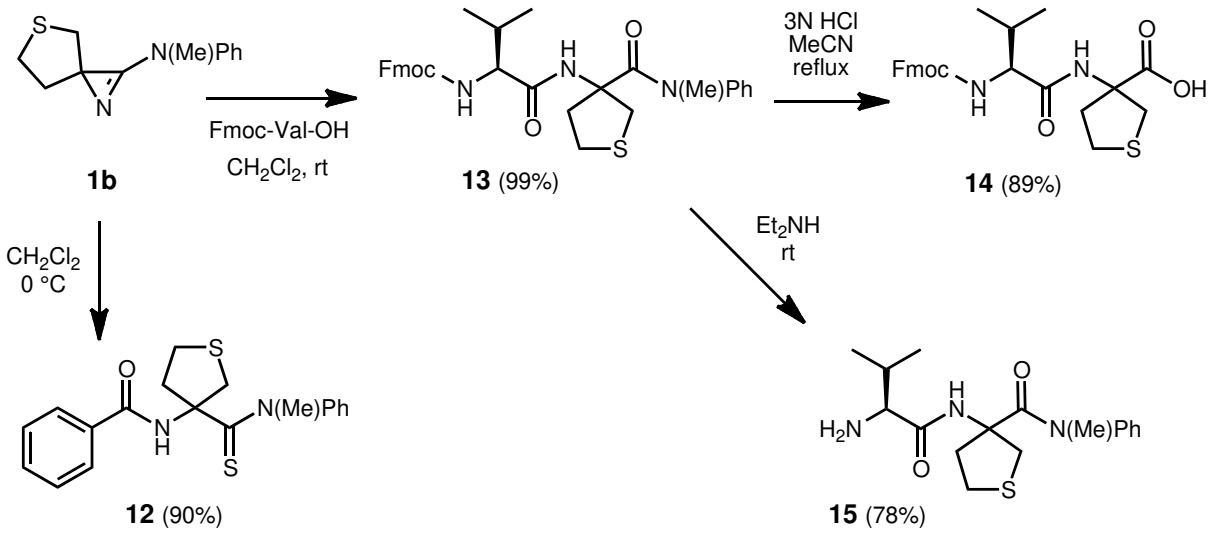
9 **10**

1b *n* = 1
1c *n* = 2

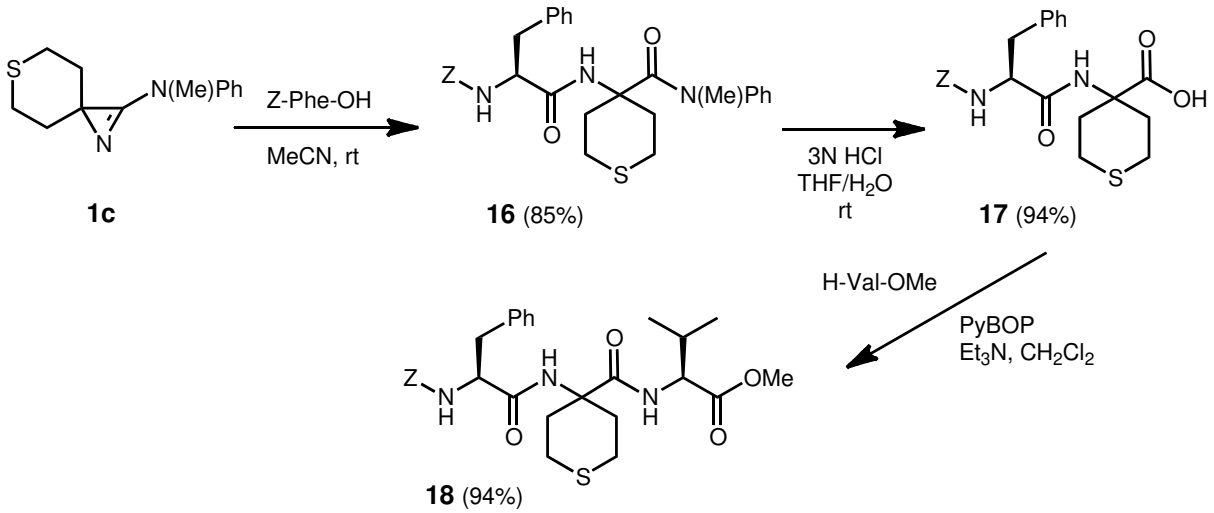
Scheme 3



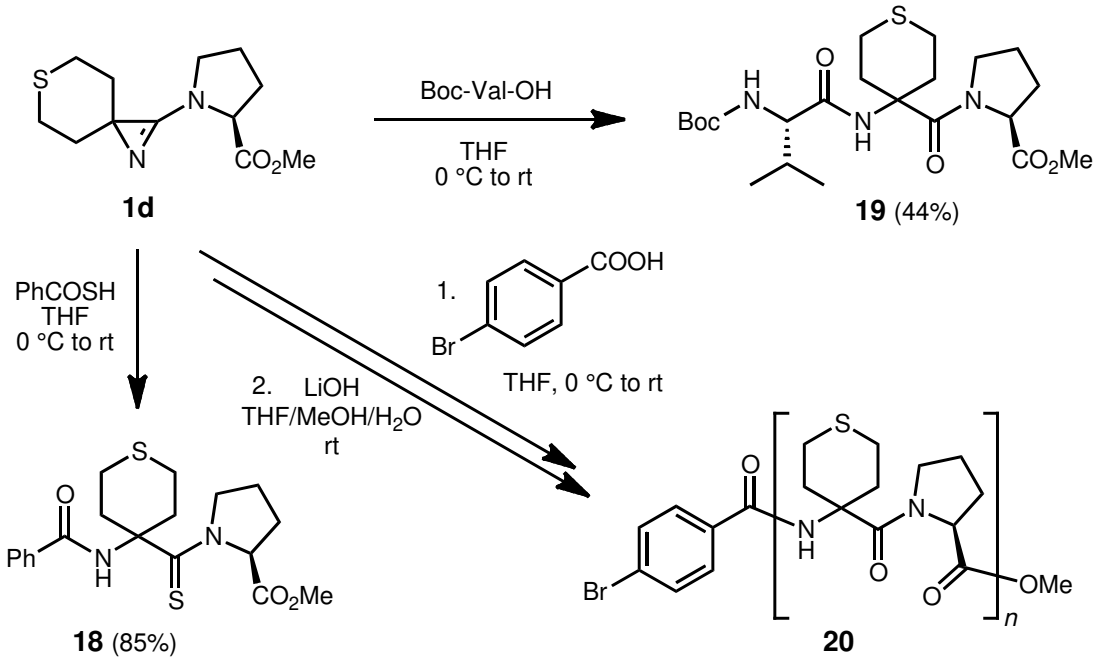
Scheme 4



Scheme 5



Scheme 6


Boc-Val-OH
THF
0 °C to rt
1d
19 (44%)
PhCOSH
THF
0 °C to rt
1.
COOH
Br
THF, 0 °C to rt
2. LiOH
THF/MeOH/H2O
rt
18 (85%)
20

Scheme 7